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(54) Ophthalmic compositions containing colchicine or vinblastine

(57) The present invention relates to a therapeutic composition comprising a topically administrable ophthalmic pharmaceutical carrier and an effective amount of an alkaloid selected from colchicine or vinblastine for temporarily alleviating the symptoms of glaucoma in humans.

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SPECIFICATION

Ophthalmic composition and method of use

TECHNICAL FIELD

The invention relates generally to a composition and method for reducing intraocular pressure (IOP) in humans and animals. More particularly, the invention relates to a method for temporarily alleviating the symptoms of glaucoma.

BACKGROUND OF PRIOR ART

Colchicine is a major alkaloid of Colchicum autumnale L., Libaceoe whose extraction procedure is well known in the art. Colchicine has been used heretofore in research on plant genetics and in the therapeutic treatment of gout and Familial Mediterranean Fever.

Vinblastine is an alkaloid isolated from Vinca rosea Linn., Apocynaceae whose extraction procedure is well known in the art. See, for example, U.S. Patent Nos. 3,097,137 and 3,225,030. Vinblastine has been used heretofore in research and as an antineoplastic agent.

Glaucoma is a condition of the eye characterized by increased intraocular pressure. Untreated, the condition eventually leads to irreversible retinal damage and blindness. Conventional therapy for glaucoma is with pilocarpine and/or epinephrine administered topically several times daily.

One of the problems with many conventional drugs for the treatment of glaucoma is that they decrease the size of the pupil, i.e., they are miotic drugs. This is an undesirable side effect, resulting in temporarily impaired vision.

BRIEF SUMMARY OF INVENTION

There has now been discovered a method of reducing IOP and for treating glaucoma in which there is a minimum of miotic side effects.

The present invention relates to a therapeutic composition comprising a topically administrable ophthalmic pharmaceutical carrier and an effective amount of an alkaloid selected from colchicine or vinblastine.

The present invention also relates to a method for reducing intraocular pressure and for temporarily alleviating the symptoms of glaucoma in humans comprising topically administering to the eyes of a human having increased intraocular pressure or having glaucoma an effective amount of the foregoing composition.

DETAILED DESCRIPTION OF INVENTION

Suitable ophthalmic carriers are known to those skilled in the art and all such conventional carriers may be employed in the present invention. Thus, a particular carrier may take the form of a sterile, ophthalmic ointment, cream gel, solution or dispersion. Also included in suitable ophthalmic carriers are slow release polymers, e.g., "Ocusert" polymers, "Hydron" polymers, etc. Stabilizers may also be used such as, for example, chelating agents, e.g., EDTA. Antioxidants may also be used, e.g., sodium bisulfite, sodium thiosulfite, 8-hydroxy quinoline or ascorbic acid. Sterility typically will be maintained by conventional ophthalmic preservatives, e.g., chlorbutanol, benzalkonium chloride, cetylpyridium chloride, phenyl mercuric salts, thimerosal, etc., for aqueous formulations, and used in amounts which are nontoxic and which generally vary from about 0.001 to about 0.1% by weight of the aqueous solution. Conventional preservatives for ointments include methyl and propyl parabens. Typical ointment bases included white petrolatum and mineral oil or liquid petrolatum. However, preserved aqueous carriers are preferred. Solutions may be manually delivered to the eye in suitable dosage form, e.g., eye drops, or delivered by suitable microdrop or spray apparatus typically affording a metered dose of medicament. Examples of suitable ophthalmic carriers include sterile, substantially isotonic, aqueous solutions containing minor amounts, i.e., less than about 5% by weight hydroxypropylmethylcellulose, polyvinyl alcohol, carboxymethylcellulose, hydroxyethylcellulose, glycerine and EDTA. The solutions are preferably maintained at substantially neutral pH and isotronic with appropriate amounts of conventional buffers, e.g., phosphate, borate, acetate, tris, etc.

A preferred ophthalmic composition is a preserved aqueous solution containing the following ingredients at the indicated concentration.

Colchicine or Vinblastine	percent	0.1
Stabilizer	"	0.01
Preservative	"	0.005
Buffer	M	0.05
NaCl q.s. ad isotronic.		

Water q.s. ad 100 percent.

The amount of colchicine or vinblastine to be used in reducing intraocular pressure and in the therapeutic treatment of glaucoma will vary with the age of the patient and the severity of the glaucoma. Generally a dose level of one or two drops of the foregoing aqueous solution 1 or 2 times daily would be a suitable dosage amount, though less, i.e., every other day dosage, also may be effective. Generally, the concentration of colchicine or vinblastine will vary between about 0.001 and about 2 and preferably between about 0.01 and 1% by weight.

It has been found that both colchicine and vinblastine administered either topically or by intra vitreal injection lowers intraocular pressure in a dose-dependent manner. A single topical application of 2 to 5 μg of either of these compounds significantly reduce intraocular pressure for more than 24 hours without signs of ocular irritation or pupillary constriction.

EXAMPLE I

A study on the effect of topical administration of colchicine and vinblastine on rabbit intraocular pressure was performed. Different amounts of colchicine or vinblastine in phosphate buffer, pH 7.5 were instilled onto the cornea of the test eye of New Zealand white rabbits at time 0, the control eye received an equal volume of the phosphate buffer without colchicine or vinblastine. IOP was measured with a pneumatic tonometer and is shown as the difference between the test and control eyes. Five animals were used for each concentration. The results for colchicine are shown in Table 1 below; the results for vinblastine in Table 2.

TABLE 1

	Change in IOP (mmHg)				
Concentration of Colchicine (%)	0	8 hrs	24 hrs	48 hrs	72 hrs
0.05	0	–0.5	–3	0	–
0.1	0	–0.5	–4	–1.5	–
0.5	0	–1	–9	–3	–0.5
2.0	0	+2.5	–9	–6	–4

The highest concentration of colchicine (2%) resulted in an initial rise in IOP, while the remaining concentrations produced a lowering of IOP without the initial rise in pressure. The lowest concentration of colchicine (0.05%) showed no ocular irritation or miosis, while the remaining concentrations showed mild ocular irritation and a slight, transient pupillary constriction. The fall in IOP at all doses was slow in onset, becoming apparent 8 hours after administration, reaching a maximum by 24 hours and then slowly returning to normal.

TABLE 2

	Change in IOP (mmHg)		
Concentration of Vinblastine	0 hrs	24 hrs	48 hrs
0.02	0	–1.4	–2.1
0.1	0	–7.5	–9.5

CLAIMS

1. A therapeutic composition for topical ophthalmic use comprising a topically administrable ophthalmic carrier and an effective, intraocular pressure reducing amount of an alkaloid selected from colchicine or vinblastine.

2. The composition as claimed in Claim 1, wherein the carrier is a preserved, substantially isotonic, aqueous solution.

3. The composition as claimed in Claim 2, wherein an effective amount of colchicine or vinblasetine is about 0.001 to about 2%.

4. The composition as claimed in Claim 1, wherein an effective amount of colchicine or vinblastine is between about 0.01 and about 1%.

5. The composition as claimed in Claim 1 comprising the following materials in approximately the indicated amounts:

Colchicine or Vinblastine	percent	0.1
Preservative	,,	0.005
Stabilizer	,,	0.01
Buffer	M	0.05

NaCl q.s. ad isotronic.

Water q.s. ad 100 percent.

6. A method for reducing intraocular pressure and temporarily alleviating the symptoms of glaucoma in humans comprising topically administering to the eye of a human having increased intraocular pressure or glaucoma a composition, the active constituent of which is an effective, intraocular pressure reducing amount of an alkaloid selected from colchicine or vinblastine and the composition containing, in addition to the compound, a suitable ophthalmic pharmaceutical carrier therefore.

7. The method of reducing intraocular pressure and temporarily alleviating the symptoms of glaucoma in humans as claimed in Claim 6, comprising administering topically to the eye of a human having increased intraocular pressure or glaucoma 1 to 2 drops of the composition of Claim 5, one to four times daily.

8. A therapeutic composition as claimed in any one of claims 1 to 5, substantially as hereinbefore described and exemplified.

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